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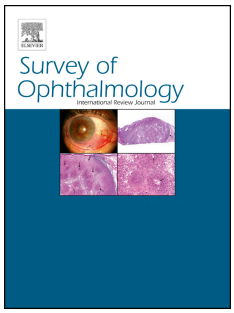

Systemic Lupus Erythematosus: an Update for Ophthalmologists

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Narrative Abstract:

Systemic lupus erythematosus (SLE) is a life-threatening multi-system inflammatory condition that may affect almost any part of the eye. We provide an update for the practicing ophthalmologist comprising a systematic review of the recent literature presented in the context of current knowledge of the pathogenesis, diagnosis and treatment of this condition. We review recent advances in the understanding of the influence of genetic and environmental factors on the development of SLE. Recent changes in the diagnostic criteria for SLE are considered. We assess the potential for novel molecular biomarkers to find a clinical application in disease diagnosis and stratification and in the development of therapeutic agents. We discuss limited forms of SLE and their differentiation from other collagen vascular disorders and review recent evidence underlying the use of established and novel therapeutics in this condition, including specific implications regarding monitoring for ocular toxicity associated with antimalarials.

Key Words:

Systemic Lupus Erythematosus, Keratoconjunctivitis sicca, Sjogren's syndrome, Lupus Retinopathy,

I. Introduction

A. Systemic Lupus Erythematosus (SLE) and the Ophthalmologist

Systemic Lupus Erythematosus (SLE) is a life-threatening multisystem autoimmune disease. Around a third of patients may have ocular involvement, ranging from relatively mild manifestations to severe, sight-threatening disease. The role of ophthalmologists in the care of these patients ranges from contributing to the acute care of a patient with severe active disease to the longer-term management of complications arising from the disease or related to its treatment.

B. Update on Epidemiology and Global Impact

1. Worldwide incidence and prevalence

The incidence and prevalence of SLE shows great variation worldwide. In their 2011 review Senga et al report annual incidence rates ranging from 0.3 to 8.7 per 100,000 per year and prevalence ranging from 1.1 to 534.9 per 100,000, with the highest incidence occurring in USA, Caribbean, Brazil and Sweden.SLE is generally less common in Europe and Asia [A.] In Europe, Caspard *et al* reported an epidemiological study for England from 1998 to 2010, noting an annual incidence of 5.5 per 100000 per year [B]. In a US study analysing 34,339 SLE patients with Medicaid coverage, Feldman et al reported an incidence of 23.2 per 100,000 per year and a prevalence of 144 per 100,000. This study found an unusually high prevalence and incidence that is likely to reflect the nature of the inclusion criteria (i.e. limited to Medicaid users) and is discussed later in this review in the context of the influence of social deprivation [28] .In contrast two state-based studies, the Georgia Lupus Registry [72] and the Michigan Lupus Epidemiology and Surveillance Program [127], identified potential cases from a wider range of sources, albeit over narrower geographical areas. The overall age-adjusted incidence rate was 5.6 per 100,000 per year for the Georgia Lupus Registry and 5.5 per 100,000 per year for the Michigan study, with an age-adjusted prevalence rate of 73 per 10, 000 reported for both studies. These studies all confirm that black race/ethnicity is associated with higher incidence and prevalence with this difference being most marked in women (see below).

2. Influence of gender

SLE predominantly affects females of childbearing age, with only 4-22% patients being male. Feldman *et al*. study found that SLE prevalence was over six times higher in women (192/100,000 for women vs 32/100,000 for men) [28]. The Georgia Lupus Registry reported age-adjusted prevalence of 128/100,000 for women vs 15/10, 000 for men, and the Michigan Lupus Epidemiology and Surveillance Program reported 129/100,000 for women and 13/100,000 for men [72,123]. As alluded to earlier, the highest risk group in all these studies are black women, with a prevalence of 286/100,000 in the Feldman study, 196/100 000 in the Georgia study, and 186/100,000 in the Michigan study.

The extent to which there is a distinct male lupus syndrome remains controversial. Some have reported a higher disease activity at presentation [96], with others suggesting that men with SLE have a more aggressive course [133], but a careful review of the literature by Murphy and Isenberg *et al.* determined that these studies often lack correction for confounders such as ethnicity or age and that overall there is limited data available for a negative prognostic association between male gender and disease activity or mortality. They do however agree that differences in system involvement between the sexes may be seen, with men being less likely to be affected by musculoskeletal symptoms, photosensitivity, oral ulcers and RP {Au: what is "RP"} than women [97,59].

3. Influence of age

Late onset SLE (>50 years) appears to run a milder course compared to childhood onset SLE [C] (<18 years). Simmons et al analyzed the influence of ethnicity and gender changes according to age of onset, with the female bias increasing across age groups [C]. Late onset SLE is particularly associated with the clinical features of pulmonary involvement and serositis. It is also more commonly associated with positive rheumatoid factor and ANA, but the significance of this is unclear since these serological markers are also more common in the non-SLE elderly population. Even though late onset SLE is associated with poorer survival, this is likely to be due to the interaction of inflammation and ageing increasing atherosclerosis [6]. In contrast to the milder course of late onset SLE, childhood onset SLE is aggressive with a higher prevalence of renal and neurological involvement and irreversible damage [D]. Anti-RNP positivity, anti-Sm positivity and a low CH50 (50% haemolytic complement) are more common in early than late onset SLE [6].

4. Influence of social deprivation

In addition to the established influences of ethnicity, gender and age, social deprivation appears to be a risk factor for SLE. In their socio-demographic analysis of Medicaid Users in the US, Feldman *et al.* found significant differences according to socioeconomic status with the highest prevalence in the lowest socioeconomic status quartile (prevalence of 168/100,000), a difference that persisted even adjusting for age, sex and race/ethnicity. They comment that the Medicaid group are a 'high-poverty group, with significant racial and ethnic minority representation.' It is likely that these two factors account for the higher incidence and prevalence seen in this cohort compared to most previous US studies [28].

5. Socioeconomic burden

SLE can have a substantial effect on the quality of life of the affected individuals. The 2013 Lupus European Online (LEO) survey which was completed by 2,070 European patients, detected that nearly 70% of patients felt the disease had affected their careers, with 27.7% changing careers within one year of diagnosis. The main complaint was reduced productivity as a result of fatigue (82.5%), with decreased ability to plan affecting all areas of daily life [42]. This decrease in productivity can lead to employment loss within 3.7 years from diagnosis in up to 57% of patients and is associated with older age at diagnosis, black race, and less education [73].

Taking all the above into account, physicians need to be aware of the serious implications that SLE has in health care planning, resource allocation and service provision.

6. Mortality

Even though survival has improved over the past forty years, the mortality rates for SLE are around four times higher than that of the general population. In a detailed analysis of a single-center cohort in Canada between 1970 and 2013, Sheane et al. found that, in the first five years since diagnosis, the leading causes of death were infection (49%) and active SLE (34%), whereas in later years death is most likely to be from infection (26%) or atherosclerotic complications (23%), with active SLE only being responsible for 15% of deaths [122].

II. Update on Pathogenesis of SLE

A. Genetic susceptibility in SLE and insights into its immunopathogenesis

SLE has a high heritability (>66%) and higher concordance rate in monozygotic compared to dizygotic twins. Sibling recurrence risk ratio is 8-29% fold compared to the general population. Genome-wide association studies (GWAS) and candidate gene studies have been performed in patients with SLE in different ethnic groups. The results show some genes are identified as risk factors in all studies regardless of the ethnic groups` studies, whereas others are specific to different ethnic populations. A recent review based on data from the National Human Genome Research Institute's Catalog of published GWAS and a PubMED search for all large scale trans ethnic or multi-ethnic studies identified 89 genes in 74 genomic regions associated with SLE [112]. Many of these genes can be linked into specific pathways to inform the pathogenesis of SLE, in association with environmental factors including ultraviolet light, smoking and infection.

A major group of genes identified in these studies (including *HLA-DR, HLA-DQ, Blk* and *PTPN22)* are all involved in immune cell signaling. *HLA-DR* and *-DQ* molecules present antigen to T lymphocytes leading to activation and cytokine production. The strongest association is HLA—DRB1*0301, a class II Major histocompatability complex molecule that presents antigen T lymphocytes. A recent meta-analysis of four independent European SLE cohorts supported a significant association of HLA-DRB1*0301 in different sub-phenotpypes of SLE [91]. *PTPN22 C1858T* is a coding polymorphism associated with increased risk of SLE. PTPN22 forms a complex with Csk, a molecule that inhibits T cell receptor signaling, leading to an increase in autoreactive cells in the periphery [91]. PTPN22 has a functional role in B cells with increased expression of Syk and PLC-2, molecules downstream of the B cell receptor leading to increased proliferation and resistance to apoptosis. Similarly, *Blk* is a B cell tyrosine receptor that signals downstream of the B cell receptor [53].

A second group of genes, including *C1q, C2, C4 FcGR2a, FcGR3a* and *ITGAM* (complement receptor 3), are involved in immune complex processing. SLE is a type III hypersensitivity response with anti-nuclear antibodies and their autoantigens forming complexes that are trapped in capillary vascular beds. Complement is a major mechanism involved in the clearance of such immune complexes. Defects in complement components, particularly C1q and C4, decreases clearance and lead to inflammation. Similarly polymorphisms in Fc-gamma receptors will also affect immune complex clearance.

A third group of genes identified in these studies (including *IRAK-1, IRF5*, *Trex1, TNFAIP3)* are related to responses to cellular damage particularly DNA. *IRF5* is one of the most frequently identified loci outside the MHC region in SLE genetics studies. IRF5 regulates expression of interferon-dependent genes and apoptosis. Recognition of DNA or single stranded RNA by Toll-like receptors (TLR) 7-9, leads via IRAK1 and type 1 interferon, to induction of *Trex1. Trex1* is a repair endonuclease that can degrade DNA from apoptotic cells. Deficiency in the clearance of damaged DNA leads to more interferon production and an inflammatory response. *TNFAIP3* encodes for the Tumor necrosis factor, alpha-induced protein 3 (TNFAIP3 protein; also known as A20), that inhibits NF-kB- mediated inflammatory responses induced by TLR. Polymorphisms in *STAT4* that encodes a signaling molecule downstream of type 1 IFN, are also associated with increased risk of SLE.

Many of the genes associated with SLE are associated with other autoimmune or autoinflammatory diseases suggesting common pathways [57]. *TREX1* polymorphisms are associated with Aicardi-Goutieres syndrome, characterized by encephalopathy and lupus-like symptoms. *TREX1* polymorphisms are highly prevalent in Cree Indians and Aicardi-Goutieres syndrome was originally described as 'Cree encephalitis' in this community. The persistence of certain mutations associated with SLE over time are based on admixture between Neanderthals and early humans, strongly indicating that these mutations have a protective effect against a common challenge, but that in combination with many other gene variants become deleterious [99].

B. Type 1 Interferons

Raised serum levels of type 1 interferons have been reported in patients with SLE. Manifestations of SLE that could be linked to raised type 1 IFN include lymphopenia, myalgia, muscle weakness, headache other neuropsychiatric problems and fatigue [101,138]. In addition, as discussed earlier, a number of IFN regulated genes have been associated with increased risk of SLE.

C. MicroRNAs and their role in immunoregulation

MicroRNAs (miRs) are conserved non-coding RNA molecules that bind to messenger RNAs to either Inhibit or degrade, controlling cell signaling and other cellular processes. A recent analysis identified 27 miRs associated with SLE. Expression of miR21 in particular was increased in $CD4^+$ T cells and strongly correlated with disease activity. Silencing of miR-21 reversed the activated phenotype of T cells from patients with SLE including the ability to induce B cell maturation into plasma cells. A potential gene target of miR21 was identified being the known tumor suppressor, programmed cell death -4 protein (PCD4). PCD4 was shown to be suppressed by miR-21 and its expression was decreased in active SLE [128]. In the context of immunoregulation, this is of interest because decreased PCD4 leads to an increase in IL-10, whereas lipopolysaccharide (LPS)-induced upregulation of miR21 inhibits this process [83,123]. Increased IL-10 via reduced PCD4 by increased miR21 would lead to increased activity in B cells and more autoantibody production. In patients with SLE, miR148a and miR126 are raised in $CD4^+$ T cells and target DNA methyltransferase-1 that is involved in methylation of genes during proliferation of cells. miR146a mediates the type 1 IFN pathway suppressing *IRAK1* and *IRF5* and its expression is inversely correlated with disease activity in patients with SLE. Many other miRs have been found in SLE, and their function will be of interest in future studies.

D. Other recent insights into the pathogenesis of SLE

The central role of the B cell in the pathogenesis of SLE is further supported by the clinical data from the novel therapeutic agent belimumab. Belimumab is a monoclonal antibody that targets TNF ligand superfamily 13B (also known as B cell activating factor [BAFF]). BAFF and a related cytokine TNF ligand superfamily 13 (also known as a proliferation-inducing ligand [APRIL]) are essential for the maturation and survival of immature B cells. Serum concentrations of both BAFF and APRIL are raised in patients with SLE. In murine studies animals induced to overexpress BAFF have high numbers of mature B cells and autoantibodies and develop a disease similar to SLE in humans [138]. Successful human trials of belimumab that causes inhibition of BAFF provides further evidence of the importance of this pathway in the disease process.

On activation, neutrophils release a fibrous net composed of DNA, proteins and small peptides from inside the cell. These structures are known as neutrophil extracellular traps (NETs) and the process as 'NETosis'. It is suggested that the primary role of NETs is to trap bacteria and fungi leading to their destruction. NETosis is a normal process, but, in patients with SLE, antibodies such as anti-RNP and anti-HNP can induce NETosis on binding to Fc□□receptors on the neutrophil surface. Moreover reduced clearance of antibodies leads to cell damage and chromatin released from damaged cells can induce IFN□ production from neutrophils which can exacerbate disease [74,110,149].

Epstein-Barr virus (EBV) has been linked to the development of SLE with patients showing a high viral titer, up 40% higher than healthy controls, in blood cells. Moreover EBV DNA is found in serum from 42% of SLE patients, compared to 3% of controls. EBV lytic replication may be linked to onset of SLE and to flares. This could link to pregnancy where inhibition of immune responses leads to release of control of EBV and SLE relapse [26]. Meta-analysis of twenty-five case controlled studies supported the link between EBV and SLE [47].

Although there is increasing knowledge of the pathways and molecules involved in SLE, there have hitherto been no clear biomarkers for diagnosis or prognosis of the disease. Recent studies are beginning to identify such biomarkers, at least for some manifestations of SLE. In one study, a 48-plex antibody array was used to identify biomarkers in patients with SLE nephritis. The results showed a decrease in C1q, and increased interleukin-6 and low density lipoprotein in initial studies [106] .In another study, serum levels of vascular cell adhesion molecule-1 (VCAM-1) and E-selectin were analysed in female patients with lupus compared to healthy individuals. E-selectin levels were raised in patients and correlated with overall tissue damage and carotid plaque, while VCAM-1 levels were associated with active renal disease [126].

III. Update on the Diagnosis of SLE

A. Current diagnostic criteria

Until recently, the diagnostic criteria for SLE were based on the 1997 update of the 1982 American College of Rheumatology (ACR) Criteria for Classification of SLE. They covered 11 domains of disease manifestations and associations [Table 1] with at least four of the eleven criteria needed to be present for diagnosis [52].

1.Malar Rash Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2.Discoid Rash Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3.Photosensitivity Skin rash as a result of unusual reaction to sunlight, by patient history or observed by physician
4.Oral Ulcers Oral or nasopharyngeal ulceration, usual painless, observed by physician
5.Nonerosive Arthritis Involving two or more peripheral joints, characterized by tenderness, swelling or effusion

6.Pleuritis or Pericarditis

A. Pleuritis- convincing history of pleuritic pain or rubbing heard by physician or evidence of pleural effusion

OR

B. Pericarditis- documented by electrocardiogram or rub or evidence of pericardial effusion

7.Renal Disorder

A. Persistent proteinuria > 0.5 gram per day or > 3+ if quantitation not performed

OR

B. Cellular casts- may be red cell, hemoglobin, granular, tubular or mixed

8.Neurologic Disorder

A. Seizures- in the absence of offending drugs or known metabolic derangements; e.g. uremia, ketoacidosis, or electrolyte imbalance

OR

B. Psychosis- in the absence of offending drugs or known metabolic derangements; e.g. uremia, ketoacidosis, or electrolyte imbalance

9.Haemotologic Disorder

A. Haemolytic anemia- with reticulocytosis

OR

B. Leukopenia- <4000/mm3 on > 2 occasions

OR

C. Lymphopenia-<1500/mm3 on >2 occasions

OR

D. Thrombocytopenia-<100000/mm3 in the absence of offending drugs

10.Immunologic Disorder

A. Anti-DNA: antibody to native DNA in abnormal titer

OR

B. Anti-Sm: presence of antibody to Sm nuclear antigen

OR

C. Positive finding of antiphospholipid antibodies on:

- an abnormal serum level of IgG or IgM anticardiolipin antibodies

-a positive test result for lupus anticoagulant using a standard method or

-a false positive test result for at least 6 months confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test

11.Positive ANA

An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs

Table 1. American College of Rheumatology (ACR) criteria

As concerns developed about the clinical criteria used in the ACR classification and the lack of validation, the SLE International Collaborating Clinics (SLICC) group formed. In 2012 they revised and validated the ACR criteria to include new knowledge and improve clinical relevance. A new classification system was produced comprising 11 clinical and 6 immunological criteria [Table 2]. For a diagnosis of SLE at least 4 criteria, including at least one clinical and one immunologic criterion, must be satisfied or the patient must have biopsy proven lupus nephritis in the presence of antinuclear antibodies or anti-double stranded DNA antibodies [108].

Clinical Criteria
1.Acute cutaneous lupus, including: Malar rash Bullous lupus Toxic epidermal necrolysis variant Maculopapular lupus rash Photosensitive lupus rash *In the absence of dermatomyositis* *OR* subacute cutaneous lupus
2.Chronic cutaneous lupus, including: Classic discoid rash Hypertrophic lupus Lupus panniculitis Mucosal lupus Lupus erythematosus tumidus Chillblains lupus Discoid lupus/Lichen planus overlap
3.Oral ulcers Palate (buccal, tongue) OR nasal ulcers *In the absence of other causes*
4.Non-scarring alopecia *In the absence of other causes*
5.Synovitis Including >2 joints, characterized by swelling or effusion OR tenderness in >2 joints and at least 30min morning stiffness
6.Serositis Typical pleurisy for more than 1 day

OR pleural effusions OR pleural rub Typical pericardial pain OR pericardial effusion OR pericardial rub OR pericarditis by electrocardiography
7.Renal Urine protein-to-creatinine ratio representing 500mg protein/24hrs OR Red blood cell casts
8.Neurologic Seizures Psychosis Mononeuritis multiplex *In the absence of other causes* Myelitis Peripheral or cranial neuropathy Acute confusional state *In the absence of other causes*
9.Haemolytic anaemia
10.Leukopenia (<4000/mm3 at least once) *In the absence of other causes* OR Lymphopenia (<1000/mm3 at least once) *In the absence of other causes*
11.Thrombocytopenia (<100000/mm3 at least once)
Immunologic Criteria
1.ANA level Above laboratory reference range
2.Anti ds DNA antibody level Above laboratory reference range
3.Anti-Sm Presence of antibody to Sm nuclear antigen
4. Antiphospholipid antibody positivity as determined by any of the following: Positive test result for lupus anticoagulant False-positive test result for rapid plasma reagin Medium or high titer anticardiolipin antibody level

Positive test result for anti-b2-glycoprotein 1
5.Low complement Low C3 Low C4 Low CH50
6.Direct Coombs test In the absence of haemolytic anemia

Table 2. SLICC Criteria

B. Update on key systemic features seen in SLE

As a multi-organ disease SLE can affect the kidneys, skin, mucous membranes, joints, CNS, lungs, heart, gut, and hematological system to variable degrees.

1. Renal

Renal involvement is one of the commonest and most serious manifestations of SLE affecting between 20-60% of the patients [E] with a higher prevalence in non-whites [F]. Lupus nephritis is not only an indicator of disease severity but is also identified as a clinical predictor of flare ups [58] . It ranges from mild, `background` glomerulo-nephritis to chronic kidney disease (CKD), with 10-30% progressing to end stage CKD within 15 years. Renal biopsy in these patients is of crucial importance, since the histopathologic findings guide the choice of treatment [19].

2. Musculoskeletal

Arthritis in SLE is common and can affect any joint with a particular predilection for the hands and knees. Surrounding tissues can be also involved with tendonitis, tendosynovitis, tendon ruptures [44] and avascular necrosis of larger joints (osteonecrosis) as well as osteoporosis secondary to steroid use [17].

3. Mucocutaneous

The skin can be involved in up to 85% of SLE and the involvement variable from disease specific malar rash, discoid rash, photosensitivity, oropharyngeal ulcers, alopecia, lupus panniculitis and lichen planus to SLE non-specific manifestations like Raynaud`s phenomenon, atrophiae blanche, bullous lesions, livedo reticularis, cutaneous vasculitis, and periungual teleangiectasias [136] .

4. Neurologic

In 1999 the American College of Rheumatology produced case definitions for 19 neuropsychiatric syndromes seen in SLE, in an attempt to standardise nomenclature. The syndromes that can affect the central or peripheral nervous system [1] are listed below [Table 3]. Headaches, cognitive dysfunction, mood disturbances and seizures are commonest in childhood SLE [105].

Central Nervous System Involvement in SLE	Peripheral Nervous System Involvement in SLE
1. Aseptic Meningitis 2. Cerebrovascular Disease 3. Demyelinating Syndrome 4. Headache 5. Movement Disorder 6. Myelopathy 7. Seizure Disorder 8. Acute Confusional State 9. Anxiety Disorder 10. Cognitive Dysfunction 11. Mood Disorder 12. Psychosis	1.Acute Inflammatory Demyelinating Polyradiculoneuropathy 2.Autonomic Disorder 3.Mononeuropathy 4.Myasthenia Gravis 5.Cranial Neuropathy 6.Plexopathy 7.Polyneuropathy

Table 3. Neurologic syndromes in SLE

5. Pleuro-Pulmonary

It has proven difficult to confirm the true prevalence of pulmonary involvement in SLE because of high rates of pulmonary infections in this group. The overall involvement is to the result of pleuritis, parenchymal changes, pulmonary vascular disease, diaphragmatic dysfunction and upper airway obstruction. A large UK series of 216 patients confirmed that 25% of SLE patients had lung involvement diagnosed clinically and/or on imaging, whereas autopsy findings confirmed up to 97% of pleuro-pulmonary involvement, with pleuritis the commonest (77.8%), followed by bacterial infections (57.8%) and alveolar hemorrhages (25.6%) [64].

6. Cardiac

The commonest cardiac manifestations of lupus are pericarditis (symptomatic in 25% of cases, and silent, autopsy-proven in up to 83%), valvular involvement confirmed by echocardiogram (up to 60%), coronary artery disease with accelerated atherosclerosis and up to 50 fold higher rate of myocardial infarction in female SLE patients and pulmonary hypertension (up to 10%). Myocarditis and endocarditis are rarer manifestations [61].

7. Gastrointestinal

Gastrointestinal (GI) symptoms are common in lupus occurring in up to 50% of patients. They tend to be mild, ranging from dysphagia, dyspepsia, abdominal pain to diarrhea [27]. Most GI manifestations are due to adverse drug reactions and infection. True lupus-related GI involvement is rarer but is potentially life threatening. Of particular importance is lupus mesenteric vasculitis (prevalence 0.2-9.7% in SLE), manifesting as acute ischemic enteritis or chronic multiple ulcers of the colon, protein-losing enteropathy (prevalence 1.9-3.2%), intestinal pseudo-obstruction and acute pancreatitis. These complications occur during active lupus, and may be a presenting feature of the disease. They tend to respond well to early diagnosis and treatment [135].

8. Haematologic

The hematological manifestations of SLE include anemia, leucopenia, thrombocytopenia and anti-phospholipid syndrome. The prevalence of hematologic disturbances and severity are variable and range from 20% [129] to 82% [121]. Up to 10% of patients can develop a severe hematologic crisis, due to hemolytic anemia or severe thrombocytopenia and this seems to be associated with more significant disease in the kidneys and CNS. It has been argued that hematological changes may be a common initial presenting feature of SLE but because of low index of suspicion or inadequate follow up, the diagnosis missed [121,129].

C. Update of the key ophthalmic features seen in SLE

Lupus can affect any part of the eye and visual system with significant impact on vision despite earlier recognition and improved treatment modalities. Ocular manifestations affect around one third of patients with SLE and may be the presenting feature of the disease [23,125]. Ocular manifestations are important both in their own right, but also because worsening ocular disease may indicate underlying systemic disease activity [103]. Within the search criteria of this article (2011-2014), there have been few recent studies which provide information on the ophthalmic features of SLE and their current prevalence in the context of improving systemic

disease control. For the reader's benefit, we present the following summary that includes these newer studies but places them within the context of the previous data on ophthalmic features in SLE. Some of this data depends on original studies prior to 2011 and/or reviews. Further details are available in a number of reviews including those of Sivaraj et al [125] and Palejwala *et al.* [103].

1. Cornea and Ocular Surface

Keratoconjunctivitis sicca or secondary Sjogren syndrome affects around 30% of patients and is the commonest ocular manifestation of SLE. Symptoms range from mild to severe, associated with a spectrum of disease encompassing corneal epitheliopathy, scarring, ulceration and filamentary keratitis [103]. Other corneal associations of SLE include recurrent corneal erosion syndrome and the potentially sight-threatening peripheral ulcerative keratitis, which is indicative of active disease [125]. Interestingly, a study on the biomechanical properties of the cornea in patients with SLE found that they have reduced corneal hysteresis and corneal resistance factor, both of which are associated with lower intraocular pressure readings by applanation [145].

2. Sclera and Uvea

Scleral involvement is rare in SLE, with scleritis or episcleritis only reported in 2.4% cases [124]. Episcleritis is generally mild and self-resolving, but the presence of scleritis is indicative of active systemic disease. Isolated anterior uveitis is rare, but may occur in the presence of scleritis and posterior inflammation [125].

3. Retina

Lupus retinopathy occurs in around 10% of patients, although the prevalence appears to be decreasing in line with better systemic management of these patients. Lupus retinopathy tends to be bilateral, but may be asymmetric. It presents with retinal hemorrhages, cotton-wool-spots, arteriolar narrowing with capillary dilation and venous dilation and tortuosity (Fig 1), as well as retinal edema, exudates and microaneurysms. It is considered to be an immune-complex vasculopathy rather than a true inflammatory vasculitis with fibrinoid degeneration and necrosis of the vessel wall [148].

Mild retinopathy may be asymptomatic and an incidental finding, whereas severe vaso-occlusive retinopathy presents with reduced vision, distortions, and visual field defects. Up to 72% of eyes can progress to neovascularization (Fig 2), with sequelae such as vitreous hemorrhage (63%), retinal traction and detachment (27%). Manifestations include central or branch retinal artery occlusions (Fig 3) and central or branch retinal vein occlusions, either combined or in isolation; 63.6% of newly diagnosed SLE patients can develop a retinal vein occlusion within four years and females under 50 years of age are at higher risk [148]. Associated antiphospholipid syndrome has previously been reported to increase the risk of both ocular and CNS vaso-occlusion by up to four times, [7]Additionally, a similar retinopathy with occlusion of major retinal vessel may be seen in primary antiphospholipid syndrome, and this diagnosis ought to be considered where there is a consistent ophthalmic picture, but an absence of typical systemic features of SLE [8].

Other rarer retinal manifestations of lupus include a retinitis pigmentosa (RP)-like retinopathy ('pseudo RP retinopathy'), choroidopathy with serous retinal detachments and frosted-branch angiitis-like vasculopathy [23,50].

4. Neuro-ophthalmic

Neuro-ophthalmic manifestations are rare and can present as unilateral or bilateral ischemic optic neuropathies (anterior and/or posterior) or with an optic neuritis that may resemble that seen in demyelinating optic neuritis [125]. Optic nerve involvement may be the presenting feature of SLE [32].

Oculomotor abnormalities may be seen, with sixth nerve palsies being the commonest [103]. Other rarer manifestations include internuclear ophthalmolplegia, nystagmus, pupillary abnormalities, light-near dissociation, blepharospasm, transient monocular visual loss, field defects, and cortical blindness [125].

5. Orbit

The orbit and periorbita are very rarely involved in SLE. Findings can include itching, madarosis, pain, edema, proptosis, enophthalmos, decreased vision, chemosis and extra-ocular muscle limitation of movement. These can be due to periorbital edema (incidence 4.8%), vasculitis, myositis and panniculitis. Orbital vasculitis is the most devastating as it may lead to visual loss. Orbital myositis may be initially misdiagnosed as bacterial cellulitis [103] and orbital panniculitis is often, but not always, associated with discoid lupus of the skin and can resolve spontaneously without cicatricial lid changes [45].

Trochleitis is a rare manifestation of orbital lupus, but may be the presentation of the disease. A recent case report describes sequential bilateral trochleitis as the presenting feature of SLE [30].

6. Intraocular infections

Because of their immunosuppressed state, lupus patients are more prone to developing infections, with nearly half developing a serious infection during the course of the disease [G]. Intraocular infections are rare, but potentially sight-threatening, including cytomegalovirus retinitis [67], acute retinal necrosis (from herpes simplex and varizella zoster viruses), tuberculous choroidal abscesses, and nocardia endophthalmitis [23].

7. Other drug induced ophthalmic complications

The most common ophthalmic side-effects of treatment are related to the use of corticosteroids and include corticosteroid-induced lens opacity (typically posterior subcapsular) and corticosteroid –induced ocular hypertension or glaucoma [115]. Additionally, the less common complication of corticosteroid-induced central serous chorioretinopathy may arise, leading to challenging therapeutic decisions as it may

be difficult to differentiate this from an SLE-induced choroidopathy [68]. Hydroxychloroquine and chloroquine may induce a sight-threatening retinopathy which is discussed later in this article.

A summary of common and uncommon ophthalmic manifestations of SLE is given below [Table 4].

Ophthalmic Manifestation	**Common**	**Uncommon**
Cornea	Keratoconjunctivitis sicca	Recurrent Erosion Syndrome Peripheral Ulcerative Keratitis
Sclera		Scleritis/Episleritis
Uvea		Uveitis
Retina	Mild Retinopathy Retinal Artery/Vein Occlusion	Severe retinopathy (neovascularization/ vitreous haemmorhage) Pseudo-RP like retinopathy Choroidopathy with Serous detachments Frosted branch angi-itis like vasculopathy
Neuro-ophthalmic blindness	6th nerve palsies	Ischemic Optic Neuropathy ischemic Optic Neuritis Internuclear Ophthalmo-plegia Pupil abnormalities Blepharospasm Transient monocular
Orbit		Vasculitis Myositis Panniculitis Trochleitis
Infection		Retinal Necrosis CMV retinopathy Tuberculous Choroidal Abscesses Nocardia endophthalmitis

Table 4. Common and uncommon ophthalmic manifestations of SLE

D. The diagnostic challenge of incomplete lupus

Lupus is characterized by heterogeneous clinical and immunological features, making the development of highly sensitive and specific classification criteria difficult. Current diagnostic criteria (ACR and SLICC), designed for the purposes of research study rather that clinical use, require four out of a relatively limited selection of clinical and immunological features [52,108] . It is widely recognized that lupus can also present with additional clinical manifestations that are not incorporated into these formal diagnostic criteria. The BILAG scoring system, that is used to quantify disease activity rather than act as a diagnostic system, recognizes a wide range of non-diagnostic features that can be part of lupus [48].

Clinically patients are often encountered who do not fulfill strict criteria for lupus. They may have a relatively mild phenotype with less than four diagnostic features or they may have disease (possibly aggressive disease) that particularly targets an organ that is not part of the diagnostic classification scheme. Ophthalmic and hepatic involvement in lupus are good examples of the latter.

Patients with milder disease that does not meet full criteria are often termed as having 'incomplete lupus erythematosus' or 'undifferentiated connective tissue disease' (UCTD). This is different from 'mixed connective tissue disease' that is an entity characterized by hard clinical features that truly overlap between defined connective tissue diseases (for example lupus and systemic sclerosis), often accompanied by anti- RNP antibodies [102]. Up to 50% of patients with connective tissue disease would fall into an UCTD category at disease onset [2]. Patients seen in clinic with UCTD features will therefore fall into three groups, those with 'stable UCTD', those with spontaneously remitting UCTD symptoms and those likely to progress to a definite CTD over a reasonable short period of time. It has been proposed that the term stable UCTD could apply to patients with a positive ANA, at least one CTD feature, and a disease duration of greater than three years [93]. Up to two-thirds of UCTD patients fall into this category [14,143]. These patients are predominantly women who remain stable over time and rarely develop life- or organ-threatening disease [95]. The commonest clinical features are Raynaud phenomenon and arthralgias, but these patients' perceived quality of life is poor [45,46,131].

For those patients in whom UCTD will evolve into a defined connective tissue disease, this will usually happen earlier in the disease course with systemic lupus erythematosus and primary Sjogren syndrome being the most common CTDs to develop. Identifying which patients will evolve is an important challenge to address. In general the presence of evolving autoantibody specificities, including antibodies to dsDNA, which have been observed to accrue prior to the onset of lupus, suggest the development of overt disease is likely [5,49,141]. A prominent interferon-induced gene signature and altered Th17/Treg ratios have been proposed as immunological markers of progression from incomplete lupus to systemic lupus erythematosus, but our understanding is limited [71,131]. Although not definitive, there is suggestive evidence that hydroxychloroquine can delay or prevent the development of full-blown lupus in patients presenting with an incomplete picture [62]. Potent immunosuppression or regular corticosteroids would not generally be used.

Patients with SLE whose disease predominantly affects a single solid organ out of proportion to other disease activity present a different challenge--and again one without a clear evidence base for treatment. We do however have a precedent from lupus nephritis that is commonly observed to involve kidneys alone. A pragmatic approach suggests that severe involvement affecting any other organ (for example liver or eye) to the extent that organ function is threatened would warrant aggressive management similar to active nephritis.

IV. Update on the Treatment of SLE

A. Principles of treatment in SLE including targets, disease monitoring and guidelines

From the perspective of disease survival, the prognosis for patients with lupus has improved dramatically since the 1950's [78]. The vast majority of patients now survive the years immediately following their diagnosis, so discussion has moved on to the definition of alternative treatment targets in order to objectively improve the outcome for patients. Suggested treatment targets have included: optimized control of inflammatory disease activity, a reduction in the accrual of permanent organ damage, a minimization of glucocorticoid exposure (and hence corticosteroid-related damage) and a reduction in longer-term mortality. Some have suggested the development of formal 'treat-to target' guidelines for lupus, analogous to those already proposed for rheumatoid arthritis [92].

1. Disease activity indices

Given than lupus is such a heterogeneous disease, an important step forward has been the development of standardised tools that allow the capture of disease activity across multiple systems. A number of tools are in existence (reviewed elsewhere [X)], the most widely used being the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and British Isles Lupus Assessment Group (BILAG) index [15, 48]. SLEDAI and subsequent derivations generate a global score of disease activity at the point of assessment (or within the last 10 or 28 days depending on version used) using a weighted system of the commonest and most severe disease manifestations in addition to routinely measured immunological parameters (anti-dsDNA antibody titres and serum complement levels). The BILAG index captures the widest range of clinical disease features. In its updated version (BILAG 2004 index) it explicitly scores activity in the last month across nine domains (constitutional, musculoskeletal, mucocutaneous, hematological, renal, abdominal, ophthalmic, cardiorespiratory and abdominal) and considers whether features are new, getting worse, same or better [55]. Comparison studies suggest both SLEDAI and BILAG indices may be used for capturing disease activity and flare in large cohorts. The BILAG 2004 index, however, has the advantage of specifically scoring rare disease manifestations such as ophthalmic lupus, with orbital inflammation, severe keratitis, scleritis, posterior uveitis, retinal vasculitis, retinal/choroidal vaso-occlusive disease, optic neuritis, and anterior ischemic optic neuropathy all counting as category A [93,146,147] features(severe and indicating that an escalation in treatment is usually required). The widely utilized system for recording the accrual of damage in lupus is the SLICC/ACR damage index [39]. Cataracts and retinal 'change' or atrophy are ophthalmic features that score in this damage index. It is important for the ophthalmologist to appreciate the distinction between clinical manifestations indicative of disease activity and those resulting from damage. For example sight-threatening corneal perforation may occur in the context of severe ocular dryness (damage) but in the absence of active inflammation (activity). Disease activity and damage may of course co-exist, but the distinction is important to help the clinician direct treatment appropriately.

2. Treatment guidelines

The most recent attempt to comprehensively review the management of lupus and issue treatment guideline based on expert opinion was published by EULAR in 2008 [11]. A similar review focusing specifically on neuropsychiatric lupus was published in 2010 [12]. Since these guidelines were published, considerable further evidence has been gathered to guide the optimal use of conventional treatment. This has particularly been the case in lupus nephritis, where the relative frequency of this disease manifestation, the ease of clearly defining disease involvement through biopsy, and the potentially catastrophic outcome of patients with active nephritis has made this group a focus for research. The accumulated evidence is such that no fewer than three nephritis-specific guidelines, KDIGO, EULAR and ACR were published in 2012 [13,46,65].

In addition to evidence supporting the use of conventional therapy, there is growing evidence to support the use of newer, targeted biological therapies in lupus. In the remainder of this review we will consider the recent advances made in the management of lupus using conventional and biological agents.

B. Conventional immunosuppressants in SLE

The current mainstay of lupus treatment is conventional immunosuppression using hydroxychloroquine, azathioprine, mycophenolate, and cyclophosphamide (and to a lesser extent methotrexate and the calcineurin inhibitors), supported by glucocorticoids. The precise mechanism of action of most of these drugs remains uncertain, and their use in lupus has derived from previous experience in treating other inflammatory diseases or from transplantation medicine. Side-effects including infection remain a significant limiting factor. Although these drugs have been used for some years now, treatment regimens continue to evolve based on growing evidence.

1. The role of anti-malarials

Traditionally considered a 'mild' lupus treatment and perhaps non-essential for many patients, accumulated data suggests multiple beneficial effects from hydroxychloroquine (HCQ) that apply to all patients. A recent comprehensive review evaluated 95 randomised controlled trials and observational studies of hydroxychloroquine in lupus [120]. Reviewed evidence concluded hydroxychloroquine reduced disease activity across the whole spectrum of severity, reduced disease activity during pregnancy, and reduced overall mortality. Evidence also supported a reduction in lupus-related thrombotic events and accumulated organ damage. Similarly anti-malarials (in this case chloroquine [CQ]) may have a role in maintaining remission in patients with previously active disease [90]. It has therefore been proposed that "hydroxychloroquine should be given to most patients with SLE during the whole course of the disease, irrespective of its severity" [120].

Retinal toxicity remains a concern, with ongoing debate as how best to monitor patients taking antimalarials for the treatment of SLE or other rheumatological conditions. Although not the primary focus of this review, this is an issue for practicing ophthalmologists and rheumatologists, and therefore we provide a brief update here. Toxicity due to HCQ remains relatively rare, but appears to be increasing in prevalence, with more recent estimates suggesting an incidence of around 1% after 5-10 years of use and rising with increased duration of use [144].

In 2011 the American Academy of Ophthalmology (AAO) published an update on recommendations for screening for CQ and HCQ toxicity advising that most patients

are routinely given 400 mg of HCQ daily "except for individuals of short stature, for whom the dose should be determined on the basis of ideal body weight to avoid overdosage". They recommend that patients get a baseline examination within the first year of use and annual screening after 5 years of use. In higher risk patients, annual screening should not be delayed till 5 years. Screening visits should include detailed ophthalmologic examination (visual acuity, corneal examination, dilated fundoscopy), automated visual field test of the central 10° (e.g. Humphrey 10-2 test) and at least one of spectral domain optical computed tomography, multifocal electroretinogram (mfERG), or fluorescein (where available) [80].

In the UK the current guidelines are the 2009 Royal College of Ophthalmologists (RCOphth) guidelines developed in collaboration with British Society of Rheumatologists and the British Association of Dermatologists which advise a maximum dosage of 6.5mg/kg/d based on lean body weight, with baseline and annual screening to include establishing the presence or absence of renal and liver dysfunction, enquiring about any visual impairment which is not corrected by refraction, and recording reading performance with a near vision chart. Referral to ophthalmologists should be done if: (1) there is suspected visual impairment at baseline which is confirmed by an optometrist, or (2) the patient notices reduced vision, patchy central vision or distorted central vision while on treatment. Recommendations for examination by ophthalmologists include tests for visual acuity and reading, central visual field (Amsler grid or automated perimetry), and slit-lamp examination of the cornea and retina. Where there is concern, evaluation may also include retinal photography, OCT, FFA and electrophysiologic tests. The UK 2009 recommendations advise: "it does not believe that the available evidence supports the introduction of a programme of systematic screening for hydroxychloroquine toxicity at the present time". Although they state that "indefinite follow-up is not likely to be required for most patients", they do advise that individual arrangements may be agreed at the local level as to whether ophthalmologists screen patients who have received > 5 years of treatment [H].

In addition to enabling earlier detection of disease, the advent of more sensitive measures of retinal structure and function have provided additional evidence of the progression of HCQ toxicity after drug cessation [87]. A number of reports emphasize that no one modality can be relied on in isolation as some patients will have functional changes (e.g. on automated visual field testing or on mfERG) before structural changes or vice versa [79,81,86].

2. The Management of Lupus Nephritis

For the induction of disease remission, all guidelines recognize the benchmark set by the original NIH trials (monthly high dose intravenous (IV) cyclophosphamide with IV methylprednisolone followed by tapering oral corticosteroids) [16]. Subsequent evidence has clearly delineated two alternatives. Firstly, the 'Euro-lupus' cyclophosphamide regimen (6 x 500mg IV cyclophosphamide pulses) has been

shown to be as effective as high dose cyclophosphamide, at least in patients of white European ancestry who do not have rapidly progressive kidney failure [54]. The equivalence of NIH and Euro-Lupus regimens in this group of patients has been demonstrated up to 10 years post treatment initiation [55]. Secondly, mycophenolate mofetil (MMF, 2-3g/day) is as effective as cyclophosphamide in inducing remission in lupus nephritis [4]. The equivalence of cyclophosphamide and MMF, but the better side-effect profile of MMF has been subsequently confirmed in study meta-analyses [63,78]. There is some suggestion MMF may be more effective in patients of a non-white European background, possibly because cyclophosphamide is less effective in this group [59].

3. The management of non-renal lupus

In contrast to the proliferation of recent trials in lupus nephritis, evidence for the optimal prescribing of traditional immunosuppressants in non-renal lupus is lacking. This is an area that has recently been reviewed elsewhere, and only trials from 2005 onwards have been discussed here [104]. Many of these trials are small, the patients are heterogeneous, and the outcome measures are highly variable and often not validated in clinical trial research. These factors make it difficult to compare studies or draw any firm conclusions. Attempting to standardize lupus trial reporting in the light of this has been highlighted [41].

For mild to moderate lupus, double-masked data supported the use of leflunomide and, in particular given the size of the study (N=215), methotrexate as a treatment and steroid-sparing agent when compared with placebo alone [31,132]. In an open label comparison of azathioprine and cyclosporin, both were equally effective as steroid sparing agents and no difference in disease activity or flare was seen between groups [43]. In an analysis of the non-renal outcomes in patients recruited to the previously discussed ALMS study of lupus nephritis (high dose IV cyclophosphamide vs. MMF) no difference in non-renal disease activity or flare was seen between groups [4,38] . This evidence that MMF is an effective treatment for non-renal lupus supports the findings of an earlier case series of 86 treated patients, and supports the conclusions of a previous review of the early mycophenolate literature [89,111]. An unmasked trial treating neuropsychiatric lupus with i.v. methylprednisone and i.v. cyclophosphamide vs. i.v. methylprednisolone alone, with oral corticosteroids in both groups suggested a better response rate at 24 months for the cyclophosphamide group [9]. An alternative cyclophophamide trial in heterogeneous cohort including neuropsychiatric, nephritis and other manifestations concluded that the traditional monthly high-dose cyclophosphamide was as effective as an even higher dose accelerated 4-day regimen. Complete response was around 50% at 30 months in both groups [107].

While the evidence is not strong enough to formulate firm guidance, it appears to support options such as methotrexate and cyclosporin in patients with mild to

moderate disease manifestation, support the use of MMF in patients with more severe disease, and support the use of traditional cyclophosphamide regimens in patients with neuropsychiatric lupus. There is of course very little specific evidence in relation to the treatment of ophthalmic lupus. The methotrexate trial had one patient with unspecified ophthalmic disease in each of the case and control arms, while the neuropsychatric lupus cyclophosphamide study has one patient with optic neuritis in the control arm and three in the treatment arm: in neither study is this sufficient to conduct an ophthalmic subgroup analysis [9,31].

C. Biological agents in SLE

Conventional treatments by no means provide a cure for lupus and can be associated with significant side effects, notably infection because of non-specific immunosuppression. As our understanding of the immunopathogenesis of lupus has grown, so has interest in the use and development of biological therapies that specifically target components of the immune system that drive disease activity.

1. Belimumab

Belimumab is a human monoclonal antibody that targets and neutralizes soluble B-lymphocyte stimulator (BLyS – also known as BAFF), a B-cell activating factor that induces B-cell proliferation and maintains survival. Efficacy in patients with moderately active non-renal lupus was assessed in two masked, randomized, placebo-controlled trials (The BLISS-52 and BLISS-76 trials) [34,100]. Most trial patients had musculoskeletal and mucocutaneous disease, and in these domains belimumab was shown to reduce disease activity and prevent disease flares. Belimumab was approved by the US Food and Drug administration in 2011, but in the UK authorization for use within the National Health Service was turned down on the basis of a cost vs. benefit decision. Follow-up of initial trial patients for up to seven years suggests ongoing efficacy and safety, but data are currently lacking for a role in lupus nephritis or more severe non-renal lupus requiring cyclophosphamide [36]. No patients with ocular disease were included in these trials, and for the moment it seems unlikely belimumab would have a role to play in managing ophthalmic complications of SLE. A trial of dual blockade of BLyS and a second B-cell survival factor called APRIL (a proliferation-inducing ligand) using the monoclonal antibody atacicept for the treatment of lupus nephritis was terminated early due the rapid development of hypogammaglobulinemia and excess infection in patients that were also given background MMF [37].

2. Rituximab

Rituximab is a chimeric anti-CD20 monoclonal antibody. Intravenous infusion leads to a rapid depletion of circulating CD20-positive mature B-cells, an effect which typically lasts a few months before reconstitution from CD20-negative B-cell precursor populations. Following anecdotal reports of efficacy in other autoimmune diseases, initial data suggesting efficacy in lupus emerged in 2002 [70]. Large open-label retrospective case series and prospective registry data suggested, and continue to suggest, efficacy in patients with lupus failing conventional therapy [24,72,113,134]. Initial enthusiasm for rituximab was curbed by disappointing results in phase III randomized controlled trials in active renal (LUNAR trial) and non-renal (EXPLORER trial) lupus [85,118]. Poor trial design and the maintenance of a high dose of corticosteroids across all patients, is likely to have played a role in the failure of these trials. Despite these studies the use of rituximab for remission induction in lupus nephritis has become standard practice in some centers [20]. Initial observational data suggesting a combination of rituximab and mycophenolate can dramatically limit the need for regular background corticosteroids is to be investigated further [20]. Emphasizing our incomplete understanding of the immunological sequelae of B-cell depletion strategies is the premature termination of a trial of ocrelizumab, a fully humanized anti-CD20 monoclonal antibody, due to unacceptable rates of serious infection in the treatment group that were also given background MMF [98]. Ocrelizumab continues to be evaluated in other disease settings.

3. Epratuzamab

Epratuzamab is a humanized monoclonal antibody targeting another B-cell antigen, CD22. In contrast to rituximab it does not induced marked B-cell depletion, but exerts complex immunomodulatory effects [114]. The phase II EMBLEM study suggested safety and efficacy over a 12-week period [140]. The underpowered ALLEVIATE study also suggested a beneficial effect and had a long (>6month) open label extension period with no additional safety concerns [139]. No patients with ophthalmic disease were recruited to these Phase II studies. Phase III studies (the EMBODY studies) are in progress.

4. Other biological agents in SLE

A considerable number of potential biological and non-biological therapeutic compounds have been investigated in pre-clinical and animal model studies. Some

have completed early phase human clinical trials, and these are summarized below Table 5.

Sifalimumab [109] Human neutralizing anti-IFNα monoclonal. Large study (n=161). Well tolerated. Efficacy trend. Trial phase ½.
Rontalizumab [82] Humanized neutralizing anti-IFNα monoclonal. Well tolerated. No disease activity data. Trial phase 1.
Sirukinamab [130] Human anti-IL-6 monoclonal. Well tolerated in humans. Murine efficacy data. Trial phase 1.
Paquinimod [10] Small molecule innate immunomodulator. Well tolerated in humans. Murine efficacy data. Trial phase 1.
Abatacept [33] (class III/IV lupus nephritis) Ig-CTLA-4 fusion protein. Large study (n=298) Well tolerated. Failed to meet primary endpoint. Trial Phase 3
Abatacept [84] (non-renal lupus) Ig-CTLA-4 fusion protein. Well tolerated but primary and secondary endpoints not met. Trial Phase 2b
N-acetylcysteine [69] Glutathione precursor. Blocks lymphocyte mTOR. Safe. Improvement in disease activity. Trial Phase ½.
Deoxyspegulin [75] Small molecule multi-target immunomodulator. Quite high dropout due to side effects. Reduction in proteinuria in lupus nephritis. Trial Phase ½.

Table 5. Other biologic agents in SLE

An additional novel approach to treatment is through the use of stem cell transplantation. There have been a number of reported cases of long lasting disease remission in previously active and treatment resistant disease using myeloablation followed by immune reconstitution with autologous hematopoietic stem cell transplantation [3]. Although perhaps effective or indeed curative, the potential risks of this therapy are likely to preclude routine use for most patients with lupus. An alternative approach has been to utilize the potential immunoregulatory effect of donor stem cells without prior myeloablation. A recent multicenter study using donor umbilical cord mesenchymal stem cell infusions in patients with active lupus refractory to conventional immunosuppression, suggested therapeutic benefit, although a number of patients relapsed after 6 months implying that repeated infusions may be needed [142].

D. Anticoagulation

Some patients with systemic lupus erythematosus also have anti-phospholipid syndrome, an acquired autoimmune condition leading to vascular thrombosis (including potential ophthalmic involvement [123]) or recurrent pregnancy failure, pre-eclampsia or placental insufficiency. Current research criteria (the Sydney criteria) for defining anti-phospholipid syndrome are outlined below [Table 6]. At least one clinical and one laboratory criteria are required to make the diagnosis [88].

Clinical Criteria	
1. Vascular Thrombosis	>1 Arterial, venous or microvascular thrombosis
2. Pregnancy morbidity	A. >1 foetal death beyond 10th week of gestation B. >3 otherwise unexplained miscarriages before 10th week of gestation C. Pre-term delivery of an otherwise normal baby before 34 weeks gestation due to eclampsia, severe pre-eclampsia or placental insufficiency
Laboratory Criteria	Must be present on 2 occasions 12 weeks apart.
1. Positive lupus anticoagulant in plasma	
2. Medium or high titer anti-cardiolipin antibodies	
3. Positive anti-β2-glycoprotein I antibodies	

Table 6. The Sydney criteria for the definition of anti-phospholipid syndrome

Recent (2012) management guidelines, based on a comprehensive review of available literature, have been published, and we would refer the reader to these for a comprehensive review of the topic [66]. While it is generally accepted that the management of primary anti-phospholipid syndrome and of anti-phospholipid syndrome in patients with SLE is no different, [35]. there are a number of controversial areas, including whether it is responsible for clinical manifestations that are not clearly a consequence of a defined thrombotic process, for example migraine or demyelination [18,56]. Similarly, there is controversy over management. A 'standard' regimen of anticoagulation (INR 2.5) has been adopted as a grade 1A evidence based guideline by some, based on randomized control trial data [21,29,66]. Others, however, have used extensive retrospective review data to propose more aggressive anticoagulation (INR 3.5) particularly in those with arterial disease, and this regimen also has its supporters [35,119]. The role of 'primary prevention' in patients with positive laboratory criteria, but no clear thrombotic history, and the treatment of patients with a suggestive clinical picture, but no abnormal laboratory tests ('sero-negative anti-phospholipid syndrome') is also unclear and beyond the scope of this review.

E. Treatment for Ophthalmic Disease

Our literature search identified no randomized controlled trials specific to the treatment of the ophthalmic manifestations of SLE, although a number of studies include ophthalmic manifestations as part of the disease activity index (such as those using BILAG 2004). Ophthalmic manifestations of SLE may be a warning that the underlying SLE is inadequately controlled and indicate that systemic treatment should be escalated (as described earlier). If there is no evidence of systemic inflammation, then some manifestations (notably ocular surface and anterior segment disease) may be adequately treated with standard topical therapies. Although there is no RCT evidence specific to these manifestations in SLE, general guidance would be a dual approach: 1) ensure that systemic control of SLE is optimized and 2) deliver best practice therapeutics/interventions for any residual features. For example in dealing with the common problem of ocular surface disease in patients with SLE, international recommendations described in the DEWS report may be used to guide the clinician in the careful assessment and hierarchical treatment of the multiple contributory factors that may lead to dry eyes [I].

Whilst RCT evidence is lacking, we found a number of recent case reports and case series of treatment of ophthalmic complications of SLE. The role of intravenous corticosteroid treatment is highlighted by two reports. Hernandez-da Mota et al reported a 16-year-old with SLE who, despite treatment with azathioprin and deflazacort, developed a frosted branch-like angiitis, which resolved after a three day course of intravenous methylprednisolone (500mg) and a tapering regime of oral prednisolone [50]. Similarly Frigui et al reported two patients presenting with bilateral visual loss, diagnosed with a bilateral optic neuritis and an ischemic bilateral optic neuropathy respectively. Both patients were extensively investigated, and an underlying systemic diagnosis of SLE made. Treatment with

intravenous methylprednisolone and tapering oral prednisolone led to a partial, but incomplete, recovery of visual function in both cases [32].

There have been a number of case reports of the use of rituximab in ophthalmic complications of SLE. In particular SLE retinal vasculitis may respond positively both in adult and children: The first report of its use in this context was by Hickman et al who reported a 33-year-old woman with sequential bilateral severe retinal vasculitis who failed to respond to intravenous methylprednisolone alone and developed second eye involvement after commencing cyclophosphamide, but subsequently went into remission on rituximab [51]. Since then Damato et al reported a 25- year-old woman who, after acute treatment with plasma exchange, went into remission and was maintained on a combination of rituximab, mycophenolate mofetil and prednisolone [22]. Similarly Donnithorne et al, presented two adolescent girls (a 16-year-old f and a 13-year-old) who, after acute treatment with intravenous methylprednisolone, were maintained on a combination with rituximab, cyclophosphamide, and oral corticosteroids [25]. Rituximab has also been reported to be successful in the treatment of SLE-associated orbital pseudotumor that had been refractory to corticosteroids and cyclophosphamide [40].

Conclusion

SLE is a life-threatening multisystem condition that is commonly associated with ocular pathology, either directly attributable to the disease or to the treatments employed. We have reviewed recent advances in our understanding of the pathogenesis, diagnosi,s and treatment of SLE relevant to the ophthalmic community. Improvements in our understanding of the genetic and environmental influences on the pathogenesis of SLE is informing the development of targeted therapies that it is hoped will control the disease more effectively with improved side-effect profiles. Although the diagnosis of SLE may be supported by testing for immunological parameters, itremains primarily clinical and thus practicing ophthalmologists should be aware of the range of manifestations of SLE. Assessment for treatment ought to be decided in conjunction with a lupus specialist, with the ophthalmologist leading on the use of topical therapy and advocating systemic escalation where the severity of the ophthalmic complications warranted it. A multi-disciplinary approach is essential for the optimal management of patients with SLE.

V. Literature search

Since this review was an update of the recent literature, a date restriction of 01 Jan 2011 onwards was used, with the searches being conducted on 01 April 2014. The following databases were searched: Medline, EMBASE, Cochrane. The search terms were: SLE, lupus, diagnostic criteria, systemic manifestations, ocular manifestations, genetics, epidemiology, quality of life, treatment, management.

Additional articles prior to this date were included where they were deemed by the authors to be of ongoing high importance (such as major guidelines that are still active) and/or critical to the understanding of the review (such as the ACR diagnostic criteria).

Captions to Images

Fig 1: Acute Retinopathy in Systemic Lupus Erythematosus with cotton-wool-spots, retinal haemmorhages, arterial narrowing and tortuosity.

Fig 2: Fundus Fluorescein Angiogram depicting vascular leakage due to neovascularization.

Fig 3: Branch retinal artery occlusion in Systemic Lupus Erythematosus.

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